REMARKS

This Amendment amends claims 11, 14 and 19, and adds new claims 23-32. The preserving and flavoring agent features of claim 11 are taken from claim 14. The "oromucosally acceptable" features of claims 11 and 14 are supported by page 2, lines 16-17 and page 3, lines 15-17. Claim 19 has been placed in independent form using the original (unamended) version of claim 11. New method of administration claims 23-32 correspond to claims 11-20. Claims 11-32 are pending.

Examiner Gembeh is thanked for allowing claims 21 and 22. This Amendment places the entire application in condition for allowance for the reasons discussed below.

This Amendment overcomes the 35 U.S.C. § 112, first paragraph, rejection of claims 11-20 for failure to adequately describe the "derivative" of formula I. Claim 11 has been amended to more clearly define its imidazole derivative as --conforming to-- formula I. Claim 19 has been amended accordingly. Reconsideration and withdrawal of the written description rejection of claims 11-20 are earnestly requested.

The 35 U.S.C. § 112, first paragraph, rejection of claims 14-17 for failure to adequately describe preserving agents, solvents

and flavoring agents is respectfully traversed. The specification describes these terms with sufficient clarity to satisfy the written description requirement. Thus, representative preserving agents include lower alkyl parahydroxybenzoates, especially methyl and propyl parahydroxybenzoate (Specification, page 2, line 32-33). Preferred solvents include alcohols, especially ethanol, and water and mixtures thereof (page 2, line 31). Preferred flavoring agents include aspartame, artificial flavors such as black currant 502.009 and mixtures thereof (page 2, last line to page 3, line 2). The specification goes on to define "additives conventionally used in oromucosal formulations" to mean any additive known by the person skilled in the art to be applicable for oromucosal formulations (page 3, lines 15-17). Accordingly, one of ordinary skill in the oromucosal dosing arts would immediately envisage what preservatives, solvents and flavoring agents would be suitable for use in the claimed oromucosal formulation. Reconsideration and withdrawal of the written description rejection of claims 14-17 are earnestly requested.

The 35 U.S.C. § 112, second paragraph, rejection of claims 14-17 is respectfully traversed. One of ordinary skill in the art would understand that "preserving agents" are intended to preserve

the useful life of the active ingredient and/or formulation. See the attached definition of "preservative" in Hawley's Condensed Chemical Dictionary (11th Ed. 1987). Reconsideration and withdrawal of the indefiniteness rejection of claims 14-17 are earnestly requested.

This Amendment overcomes the 35 U.S.C. § 102(b) rejection of claims 11-13 over U.S. Patent No. 5,498,623 to Karjalainen et al. The claimed composition includes at least one oromucosally acceptable preserving agent, at least one flavoring agent or a mixture thereof. Karjalainen et al. fails to disclose these features of the claimed composition. Reconsideration and withdrawal of the anticipation rejection of claims 11-13 are earnestly requested.

The 35 U.S.C. § 103(a) rejection of claims 11-17, 19 and 20 over Karjalainen et al. in view of U.S. Patent No. 5,658,938 to Geerts et al., U.S. Patent No. 6,326,401 to Chauveau et al. and Huupponen et al., 58 Clin.Pharmacol.Ther. 506-11 (1995) is respectfully traversed. Oral administration of a substituted imidazole derivative conforming to formula (I) has been associated with compromised cardiac safety (Specification, page 1, line 31 to

page 2, line 2) and rapid decomposition of the derivative (Page 1, lines 24-30).

The applicants have discovered these problems of compromised cardiac safety and rapid decomposition can be avoided by oromucosal administration. Thus, Example 8 reports a study of cardiac safety in dogs in which fipamezole orally administered indicated QT prolongation would occur when the systemic concentration of the drug reached about 2000 ng/ml. Yet two toxicology studies showed no signs of compromised cardiac safety when fipamezole was administered by buccal spray doses. This is very surprising because one would expect that cardiac safety would be more compromised when fipamezole was administered oromucosaly because the drug would reach the heart directly through the circulatory system instead of passing through the liver before reaching the heart, as in the case with oral administration.

Example 7 of the application illustrates the significant increase in plasma levels of fipamezole in healthy male volunteers which is achieved by oromucosal administration in comparison to oral administration. Table 1 compares the pharmacokinetic parameters of fipamezole at the dose level of 30 mg resulting from oral administration, oromucosal tablet and oromucosal spray

administration, while Figure 1 plots mean plasma concentration over time following a single, 30 mg dose of fipamezole. In short, oromucosal adminstration was shown to result in much higher plasma concentrations of fipamezole than achieved by oral administration.

None of the cited combination of references disclose or suggest the claimed invention. Neither Karjalainen et al. nor Geerts et al. disclose an ormucosal formulation. Chauveau et al. merely discloses the utility of capryl caproyl macrogèl glycerides in delivering tryptan-like non-polypeptide substances via buccal administration. Finally, Huupponen et al. differs from the claimed invention because atipamezole does not contain a halogen or hydroxyl at R_1. Neither halogen or hydroxyl are bioisoteric with the hydrogen in atipamezole. Thus, the subject matter of the claims cannot be considered obvious to one of ordinary skill. See the International Preliminary Examination Report.

Reconsideration and withdrawal of the obviousness rejection of claims 11-17, 19 and 20 are earnestly requested.

The provisional obvious-type double patenting rejection of claims 11-17 and 19 over claims 1-3 and 12-18 of U.S. application S.N. 10/534,117 is respectfully traversed. This application was filed first, and has been examined. In contrast, the '117

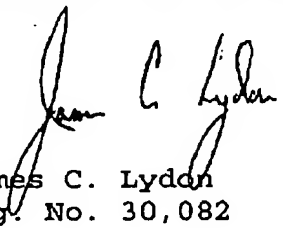
application has not yet been examined. As demonstrated above, this application is otherwise in condition for allowance. Accordingly, the Examiner is requested to withdraw the provisional rejection and permit this application to issue. A corresponding, non-provisional obvious-type double patenting rejection can then be made in the '117 application, if appropriate.

It is believed the application is in condition for allowance. Reconsideration and withdrawal of all rejections of claims 11-20, and issuance of a Notice of Allowance directed to claims 11-32, are respectfully requested. The Examiner is urged to telephone the undersigned should she believe any further action is required for allowance.

An Excess Claim Fee Transmittal is attached. It is not believed any additional fee is required for entry and consideration of this Amendment. Nevertheless, the Commissioner is authorized to

charge our Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,



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Enclosures:
Hawley's Condensed Chemical Dictionary 965 (11th Ed. 1987)
Excess Claim Fee Transmittal

Hawley's Condensed Chemical Dictionary

ELEVENTH EDITION

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ble in organic solvents, not precipitated by digitonin.
Derivation: Isolation from urine of pregnant women, cows, mares, and chimpanzees; by reduction of pregnanedione.
Use: Synthesis of progesterone, medically as a pregnancy test.

pregnenedione. See progesterone.

pregnenisolone. See ethisterone.

4-pregnen-21-ol-3,20-dione. See deoxycorticosterone.

pregnenolone. (Δ^5-pregnene-3β-ol-20-one).
CAS: 145-13-1. $C_{21}H_{32}O_2$. A steroid which is a biologically active hormone similar to progesterone and the adrenal steroid hormones.
Properties: Crystals in needles from dilute alcohol, mp 193C. Slightly soluble in acetone, petroleum ether, benzene, and carbon tetrachloride.
Derivation: From stigmasterol or other steroids.
Use: Medicine, biochemical research. Also available as acetate salt.

Prelog, Vladimir. (1906-) A Swiss organic chemist who won the Nobel prize for chemistry in 1975 along with Cornforth for work on chemical synthesis of organic compounds. Although educated in Yugoslavia, his most recent years have been spent in Zurich.

premix molding. A mixture of plastic ingredients prepared in advance of the molding or extruding operation and stored in bags or bins until required. They are made by mixing the components (resin, filler, fibrous materials such as glass and necessary curatives) in a dough blender. Storage life may be from a few days to a year or more, depending on formulation. Such mixtures are then calendered or extruded after warming to suitable temperature.

prenitene. (1,2,3,4-tetramethylbenzene; prenitol). $(CH_3)_4C_6H_2$.
Properties: Colorless liquid, soluble in alcohol, insoluble in water, d 0.901, bp 204C, fp −7.7C.

prepolymer. An adduct or reaction intermediate of a polyol and a monomeric isocyanate, in which either component is in considerable excess of the other. A polymer of medium molecular weight having reactive hydroxyl and —NCO groups.
Use: Preparation of polyurethane coatings and foams.

prepreg. A term used in the reinforced plastics field to mean the reinforcing material containing or combined with the full complement of resin before molding.

"Pre-San."[7529] [N-(2-mercaptoethyl)benzenesulfonamide-S-(O,O-diisopropylphosphorodithioate)]. TM for a selective herbicide.

preservative. Any agent that prolongs the useful life of a material. Food products are preserved by (1) low temperature, (2) ionizing radiation (x- and gamma rays), and (3) antioxidants and similar additives. Antioxidants are also used in lube oils, rubber, and plastics; fungicides on textiles; aldehydes on biological specimens; paints on wood and metals.
See also protective coating; antioxidant; radiation, industrial.

press, hydraulic. See hydraulic press.

"Prestabit Oil" V. TM for an anionic textile chemical consisting of purified sulfated castor-oil fatty acids.
Use: Dyeing assistant for cotton and wool fiber, in viscose manufacture; clarifying agent to prevent milkiness of the yarn, antistatic agent for acetate and polyacrylonitrile fibers.

Prevost reaction. Hydroxylation of olefins with iodine and silver benzoate in an anhydrous solvent to give trans-glycols.

Priestly, Joseph. (1733–1804) Born near Leeds, England. Priestley originally planned to enter the ministry. As a youth he became interested in both physics and chemistry and his research soon established his position as a scientist. He was elected to the Royal Society in 1766. He discovered nitrous oxide in 1772 but his greatest contribution to science was his discovery of oxygen in 1774. He emigrated from England to Northumberland, PA, where he lived from 1784 to his death. His research in America resulted in the discovery of carbon monoxide (1799).

Prigogine, Ilya. (1917-) A Belgian chemist who won the Nobel prize for chemistry in 1977 for his contributions to nonequilibrium thermodynamics. His education was at the University of Brussels. The Center for Statistical Mechanics and Thermodynamics at the University of Texas bears his name.

Prilezhaev (Prileschajew) reaction. Formation of epoxides by the reaction of alkenes with peracids.

prills. Small round or acicular aggregates of a material, usually a fertilizer, that are artificially